AD-A170 368 EVALUATION OF PHARMACOLOGIC AGENTS TO SUPPRESS INTRAOCULAR CELLULAR PROLI (U) MICHIGAN STATE UNIV EAST LANSING DEPT OF SURGERY G L BLANCHARD ET AL. 1/1

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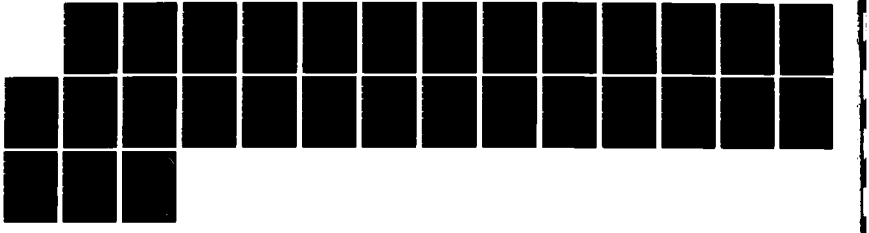

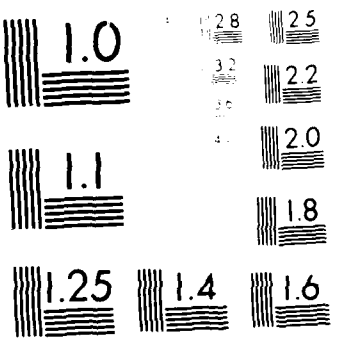
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EVALUATION OF PHARMACOLOGIC AGENTS TO SUPPRESS INTRAOCULAR CELLULAR PROLIFERATION FOLLOWING TRAUMA

ANNUAL REPORT

September 1983 (Revised July 1986)

Michael T. Trese, M.D.
Hedwig A. Seski Murphy, M.D.
Gary L. Blanchard, D.V.M.

SUPPORTED BY

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland 21701-5012

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MICHIGAN STATE UNIVERSITY
COLLEGE OF HUMAN MEDICINE
DEPARTMENT OF SURGERY

East Lansing, Michigan 48824-1315

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19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

5-FU	indomethacin
methyltrexate	colchicine
prostaglandin PGE1	d-penicillamine
dexamethasone	similar experimental conditions
triamcinolone	clinical-pathologic results

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

In an animal model of tractional retinal detachment using both labeled and unlabeled retinal pigment epithelial cells, we determined that methyltrexate and 5-FU were the most effective currently considered pharmacologic agents for the suppression of intraocular cellular proliferation based upon suppression of clinical tractional retinal detachments.

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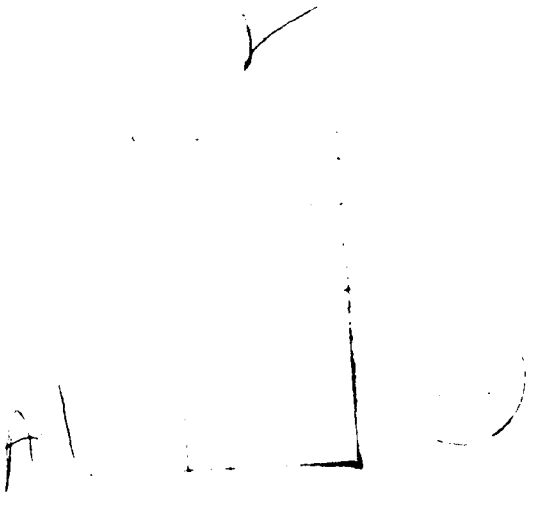
Block 20: Abstract
Following trauma to the eye intraocular cellular proliferation is the most common cause of tractional retinal detachment and subsequent loss of the globe if the eye survives the initial trauma. This study has been designed to test various pharmacologic agents to suppress intraocular cellular proliferation and reduce tractional retinal and ciliary body detachment and subsequent loss of the eye form either retinal detachment or cyclitic membrane formation. The course of year's activity centered around evaluation of the model induced tractional retinal detachments in both control eyes and eyes treated with the pharmacologic agents (triamcinolone,dexamethasone prostaglandin PGE1, methyltrexate, 5-FU and colchicine). The eyes were studied in a gross and light microscopic fashion in addition to transmission electron microscopy. Previously we have studied colchicine and although it has a very appealing mechanism involving the microtubular systems of dividing cells, it also affects the microtubular system of nondividing cells and although effective in a very low dose, its toxic dose is very close to its therapeutic dose. Of the eyes examined to date, it appears that the 5-FU group of eyes shows the most effective reduction in cellular proliferation with the least amount of retinal damage and we presume therefore the best functional result. All of these drugs were used in an intravitreal fashion although possibly subconjunctival administration of some of the drugs may be effective although this was not tested in this study. We feel at this time that based upon our review of these drugs from a histologic and clinical standpoint that 5-FU appears to be the most promising intravitreal pharmacologic agent with the safest range between toxic and therapeutic dose.



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SUMMARY

Since the original descriptions of Gonin, the emphasis on repair of retinal detachment and trauma involving the posterior pole of the eye has been centered on the development of mechanical devices and the techniques to eliminate forces which dislodge the retina from its normal anatomic position. The techniques of scleral buckling and more recently, vitreous surgery, membrane peeling and divisions of subretinal strands, have rapidly proliferated and developed to a very sophisticated level. Even with these highly sophisticated vitreo-retinal techniques, still many eyes each year are lost to proliferative vitreoretinopathy and fibrous ingrowth secondary to trauma. The pioneering work of Machemer and Laqua demonstrated to us that these tragic ocular events were due to proliferating cells throughout the vitreous scaffolding or along the anterior and posterior retinal surfaces.[1] Based on the concept of a surgical and chemotherapeutic approach to cellular proliferation elsewhere in the body, it has been suggested by many that adjunctive pharmacologic therapy be used to suppress intraocular cellular proliferation. To this end, both dexamethasone and triamcinolone have been suggested and tested under different experimental techniques. Other drugs, such as methyltrexate, d-penicillamine, colchicine, prostaglandin PGE1, and indomethacin, have been suggested.[2,3,4] No study has to date made an attempt to test all of these drugs under identical experimental conditions. Both the clinical suppression of retinal detachment as well as the relative toxic features of each pharmacologic agent is assessed in this study.

FOREWORD

In conducting the research described in this report, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication NO. (NIH) 78-323, Revised 1978.)

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MATERIALS AND METHODS

Ninety-nine Dutch belted rabbits weighing between 2 and 3 kg were used for this study. Nine rabbits (18 eyes) were used for harvesting of retinal pigment epithelial cells. This was achieved by standard techniques. The eyes following harvesting, had the anterior segment removed, including the lens. This left a posterior eye cup. The vitreous and retina were removed under sterile conditions under a laminar flow hood. Quarter percent Trypsin was irrigated into the eye cup following removal of the vitreous and neurosensory retina. The cells were then placed in Hamm's F-10 media with 10% fetal calf serum. Following this, the cells were inspected by inverted microscopy and placed in an incubator. The cells from two eyes were labeled with tritiated thymidine for labeled retinal pigment epithelial cell injection. Following this, animals were divided into groups of ten for injection of pharmacologic agents as well as control groups. The animals underwent a lensectomy, vitrectomy using a mini-nibbler vitreous instrument under sterile conditions in the surgical center of the Veterinary School of Michigan State University. At the end of the surgical procedure, the control groups received injection of 75,000 unlabeled retinal pigment epithelial cells, to a group of five eyes. The same procedure, including injection of retinal pigment epithelial cells, was then performed into eight other groups of five eyes. To one eye in each group of five labeled retinal pigment epithelial cells were injected as opposed to unlabeled as in the other four eyes of each group. Immediately following injection of retinal pigment epithelial cells in this

group, pharmacologic agents were injected. The following dosages were used: dexamethasone 2 mg, triamcinolone 2 mg, 5-FU 2 mg, methyltrexate 2 mg, prostaglandin PGE1 2 mg, d-penicillamine 2.5 mg, 50 ug colchicine and 1 mg of indomethacin. Each of these doses were prepared without preservatives and at stable pH and delivered in a 0.1 cc volume. The animals were followed initially at the first four hours with hourly indirect ophthalmoscopy and following that they were followed at daily intervals of one week and then weekly intervals until sacrificed. Animals in the control group received the same observation schedule. The animal with labeled cells was sacrificed at one week in this group. The other animals were sacrificed at two weeks. four weeks, six weeks and three months. The eyes were removed for light microscopic as well as scanning and electron microscopic study and autoradiography. The second phase of this study involved identical surgical procedures and injection of cells. However, drugs were injected in the same dosage at one week following injection of retinal pigment epithelial cells in an attempt to determine if a particular drug may be more effective at the one week interval when cells which can cause tractional retinal detachment have already achieved some footing. ERG's were done preoperatively as well as at two week intervals postoperatively until the animal was sacrificed as an index to drug toxicity.

Following fixation and prior to embedding, each eye was opened and studied in a gross fashion to determine the gross appearance of

retinal position, areas of cellular proliferation. These eyes have been submitted for light scanning and transmission electron microscopy to assess the morphologic integrity of the neurosensory retina as well as the membranous material as an index of both drug toxicity and drug efficacy.

RESULTS

The results of the clinical examinations on both control and drug injected animals are presented in Tables 1-9.

TABLE I

CONTROLS

animal #	2 day post op uveitis (1-4)	pharm. agent or control	Clinical Tractional Detachment*					Gross Exam**
			1 wk	2 wk	4 wk	6 wk	12 wk	
Immediate injection of drug								
1	2	C	+	/ SACRIFICED /				+
2	1	C	+	+	//	//	//	+
3	2	C	+	+	+	//	//	+
4	2	C	+	+	+	+	//	+
5	Blood	C	NO VIEW					Total detach. Vit. bleed
One week later injection of drug								
6	2	C	+	//	//	//	//	+
7	Corneal Haze 3	C	+	+	//	//	//	+
8	2	C	+	+	+	//	//	+
9	1	C	+	+	+	+	//	+
10	3	C	+	+	+	+	+	+

Legend:

* Clinical Detachment included puckering of medullary ray and peripheral detachmen weeks after drug injection

** Done following enucleation

TABLE 2

5-FU 2 mg

animal #	2 day post op uveitis (1-4)	pharm. agent or control	Clinical Tractional Detachment*					Gross Exam**
			1 wk	2 wk	4 wk	6 wk	12 wk	
Immediate injection of drug								
11	3	5-FU	-	/ S A C R I F I C E D /				-
12	1	5-FU	Corn. Haze	-	//	//	//	-
13	1	5-FU	-	-	-	//	//	-
14	1	5-FU	Corn. Haze	Corn. Haze	-	-	//	-
15	2	5-FU	Corn. Haze	-	+	+	+	+ Retinal Hole
One week later injection of drug								
16	2	5-FU	Corn. Haze	//	//	//	//	-
17	2	5-FU	-	-	//	//	//	-
18	2	5-FU	+	+	+	//	//	+
19	3	5-FU	+	+	+	+	//	+
20	3	5-FU	-	-	-	-	-	-

Legend:

* **Clinical Detachment included puckering of medullary ray and peripheral detachment weeks after drug injection**

** **Done following enucleation**

TABLE 3

METHYLTREXATE 2 mg

animal #	2 day post op uveitis (1-4)	pharm. agent or control	Clinical Tractional Detachment*					Gross Exam**
			1 wk	2 wk	4 wk	6 wk	12 wk	
Immediate injection of drug								
21	2	M	-	/ S	A C R	I F I	C E D /	-
22	1	M	-	-	//	//	//	-
23	3	M	-	-	-	//	//	-
24	1	M	-	-	-	-	//	-
25	1	M	-	-	-	-	-	-
One week later injection of drug								
26	3	M	No View	//	//	//	//	-
27	2	M	Corn. Haze	-	//	//	//	-
28	1	M	-	-	+	//	//	+
29	2	M	Corn. Haze	N O	V I E	W	//	-
30	1	M	N O	V I E	W			+

Legend:

* Clinical Detachment included puckering of medullary ray and peripheral detachmer weeks after drug injection

** Done following enucleation

TABLE 4

COLCHICINE 50 mg

animal #	2 day post op uveitis (1-4)	pharm. agent or control	Clinical Tractional Detachment*					Gross Exam**
			1 wk	2 wk	4 wk	6 wk	12 wk	
Immediate injection of drug								
31	3	C	Orange Reflex	/ S A C R I F I C E D /				Retinal Necrosis
32	3	C	Orange Reflex	No View	No View	//	//	Retinal Necrosis
33	3	C	Orange Reflex	No View	No View	//	//	Retinal Necrosis
34	3	C	Orange Reflex	N O	V I E W		//	Retinal Necrosis
35	3	C	Orange Reflex		N O	V I E W		Retinal Necrosis
One week later injection of drug								
36	3	C	Orange Reflex	/ S A C R I F I C E D /				Retinal Necrosis
37	2	C	Orange Reflex	No View	//	//	//	Retinal Necrosis
38	2	C	N O	V I E W		//	//	Retinal Necrosis
39	3	C		N O	V I E W		//	Retinal Necrosis
40	2	C			N O	V I E W		Retinal Necrosis

Legend:

* Clinical Detachment included puckering of medullary ray and peripheral detachmen
weeks after drug injection

** Done following enucleation

TABLE 5

INDOMETHACIN 1.0 mg

animal #	2 day post op uveitis (1-4)	pharm. agent or control	Clinical Tractional Detachment*					Gross Exam**
			1 wk	2 wk	4 wk	6 wk	12 wk	
Immediate injection of drug								
41	3	I	No View	/ S A C R I F I C E D /				+
42	3	I	No View	+	//	//	//	+
43	4	I	N O	V I E W	+	//	//	-
44	3	I	No View	+	+	+	//	+
45	3	I	No View	+	+	+	+	+
One week later injection of drug								
46	A N E S T H E T I C			D E A T H				
47	3	I	No View	//	//	//	//	+
48	3	I	N O	V I E W	//	//	//	+
49	3	I	No View	+	+	+	//	+
50	4	I	No View	+	+	+	+	+

Legend:

* Clinical Detachment included puckering of medullary ray and peripheral detachm
weeks after drug injection

** Done following enucleation

TABLE 6

D-PENICILLAMINE 2.5 mg

animal #	2 day post op uveitis (1-4)	pharm. agent or control	Clinical Tractional Detachment*					Gross Exam**
			1 wk	2 wk	4 wk	6 wk	12 wk	
Immediate injection of drug								
51	3	DP	No View	/ SACRIFICED /				+
52	3	DP	NO	VIEW //		//	//	-
53	2	DP	NO VIEW			//	//	Coagulation Necrosis
54	3	DP	NO	VIEW +		+	//	+
55	3	DP	No View	±	+	+	+	+
One week later injection of drug								
56	3	DP	No View	/ SACRIFICED /				+
57	2	DP	No View	±	//	//	//	-
58	3	DP	NO VIEW			//	//	-
59	3	DP	No View	±	-	-	//	-
60	3	DP		NO VIEW			+	+

Legend:

* **Clinical Detachment included puckering of medullary ray and peripheral detachment weeks after drug injection**

** **Done following enucleation**

TABLE 7

DEXAMETHASONE 2 mg

animal #	2 day post op uveitis (1-4)	pharm. agent or control	Clinical Tractional Detachment*					Gross Exam**
			1 wk	2 wk	4 wk	6 wk	12 wk	
Immediate injection of drug								
61	1	D	-	/ S A C R I F I C E D /				-
62	1	D	-	-	//	//	//	-
63	1	D	-	-	-	//	//	+
64	D I E D P O S T OP							
65	1	D	-	+	+	+	+	+
One week later injection of drug								
66	2	D	+	/ S A C R I F I C E D /				+
67	3	D	+	+	//	//	//	+
68	3	D	-	-	-	//	//	-
69	2	D	+	+	+	+	//	+
70	3	D	+	+	+	+	+	+

Legend:

* Clinical Detachment included puckering of medullary ray and peripheral detachmen weeks after drug injection

** Done following enucleation

TABLE 8

TRIAMCINOLONE 2 mg

animal #	2 day post op uveitis (1-4)	pharm. agent or control	Clinical Tractional Detachment*					Gross Exam**
			1 wk	2 wk	4 wk	6 wk	12 wk	
Immediate injection of drug								
71	0	T	-	/ SACRIFICED /				-
72	0	T	-	-	//	//	//	-
73	0	T	-	+	+	//	//	+
74	0	T	-	-	+	+	//	+
75	0	T	-	+	+	+	+	+
One week later injection of drug								
76	2	T	+	/ SACRIFICED /				+
77	3	T	+	+	//	//	//	-
78	2	T	+	+	+	//	//	+
79	1	T	-	-	-	-	//	-
80	2	T	+	+	+	+	+	+

Legend:

* Clinical Detachment included puckering of medullary ray and peripheral detachme
weeks after drug injection

** Done following enucleation

TABLE 9

PROSTAGLANDIN PGE1 2 mg

animal #	2 day post op uveitis (1-4)	pharm. agent or control	Clinical Tractional Detachment*					Gross Exam**
			1 wk	2 wk	4 wk	6 wk	12 wk	
Immediate injection of drug								
81	2	-	-	/ SACRIFICED /				-
82	1	P	-	+	//	//	//	-
83	2	P	-	+	+	//	//	+
84	1	P	+	+	+	+	//	+
85	ANESTHETIC DEATH							
One week later injection of drug								
86	2	P	-	/ SACRIFICED /				-
87	3	P	+	+	//	//	//	+
88	3	P	+	+	+	//	//	+
89	2	P	-	-	-	-	//	-
90	3	P	-	-	-	-	-	-

Legend:

* Clinical Detachment included puckering of medullary ray and peripheral detachm weeks after drug injection

** Done following enucleation

DISCUSSION

With the advent of the sophisticated techniques of retinovitreal surgery, many eyes which would have been previously lost have been saved. However, still a large number of eyes succumb to intraocular cellular proliferation following chronic retinal detachment and trauma. For this reason, pharmacologic therapy has been investigated by several authors. The mode of pharmacologic action is widely diversified in the approaches of many investigators. The experimental models have been dissimilar and therefore, it has been very difficult to compare in a side-by-side fashion which pharmacologic agent represents the best pharmacologic alternative. Most of these studies have been done in rabbit models with a medullary ray and avascular retina. The purpose of our study was to analyze each pharmacologic agent in terms of its mode of operation and to test it side-by-side with the other available pharmacologic agents to see which had the most marked clinical response as well as which caused the least tissue damage. We used for our model an injected bolus homologous retinal pigment epithelial cells. These cells were grown in tissue culture and in some cases, for each drug labeled with tritiated thymidine. When the eyes were evaluated clinically, it became apparent that the one drug, colchicine, was very toxic to the eye and caused an extensive tissue necrosis in a majority of eyes, whether injected (at the time of injection of retinal pigment epithelial cells) or late (one week following injection to retinal pigment epithelial cells). Two to the drugs, 5-FU and methyltrexate, showed an excellent clinical response with the vast

majority of eyes injected with both of these drugs not undergoing clinical detachment, but seeming to be more effective when injected immediately after injection of retinal pigment epithelial cells than the one week after the injection of cells. Prostaglandin PGE1 and d-penicillamine showed a more favorable response than other drugs when injected at one week following injection to retinal pigment epithelial cells. These drugs have a comparable effect at that point with methyltrexate and 5-FU.

Dexamethasone and triamcinolone showed quieting of uveitis when compared with control groups. However, they did not show a significant reduction in clinical detachment. Indomethacin was like colchicine, totally ineffective.

When we explore the mode of operation of each of these pharmacologic agents these results are reasonable. The direct cytotoxic effect of 5-FU and methyltrexate could be anticipated to be most active in the proliferating cells immediately following injection of the retinal pigment epithelial cell bolus. The 5-FU and methyltrexate might continue to have an effect when given to the one week post cell injection eyes due to the fact that there will be a number of cells at that point which should still be proliferating. This seems to fit well with our observation that methyltrexate and 5-FU suppressed clinical detachment more effectively in the immediate injection than it did at the one week injection group although it still showed good clinical response at one week post injection. If we then examine the effects of

prostaglandin PGE1 which we have anticipated would block the contraction of myofibroblasts, we find that this drug is more effective when given at the one week post injection interval. We can suggest that this is due to an effect on myofibroblasts which take some time to develop within the cell bolus following injection. In previous studies with injection of retinal pigment epithelial cells, we have identified myofibroblasts and, therefore, it seems reasonable that prostaglandin PGE1 may have an effect on that cell population. D-penicillamine which is suggested to interact with cell-to-cell junctions might also be anticipated to have a larger effect in the eyes in which the drug is injected one week after the retinal pigment epithelial cells. Indomethacin showed no difference in the rate of clinical detachment than our controls alone. Dexamethasone and triamcinolone showed a better response in the eyes in which the drugs were given immediately after cell injection than at the one week interval. However, neither drug was clinically as effective as 5-FU and methyltrexate. Colchicine was tolerated worst by the rabbit eyes. Its anti-microtubial effect seemed to cause a generalized intraocular necrosis which was very marked, even in a very small dose. This drug seems to have no role in terms of clinical suppression of intraocular cellular proliferation.

Clinical observations showed that a transient corneal opacification was present with the use of 5-FU. The cornea became cloudy and then cleared after forty-eight hours generally and in no eye was lasting corneal opacity present, and by the time of

harvesting of eyes even at the one week interval, the cornea had regained clarity. The electroretinogram was performed in representative animals in each group. Difficulty of interpretation of rabbit electroretinography is well known and therefore, for that reason, an electroretinogram was termed abnormal only if a flat line ERG was generated. The only animals post injection to develop such a flat line ERG were the colchicine eyes which showed clinical toxicity far greater than any other study drug. Our data indicates that dexamethasone and triamcinolone, although showing an excellent quieting effect on the initial uveitis and initial suppression of detachment does not give a lasting suppression of detachment.

From our clinical results, both 5-FU and methyltrexate seem to be the drugs of choice certainly if administered very close to the time of trauma. It may be, however, that the consideration of a multi-pharmacologic bolus injection is more applicable to the clinical situation in humans. In the clinical circumstance where a patient experiences trauma, a cell bolus is immediately made available to the vitreous cavity. The eye initially undergoes anterior segment or scleral repair. Ryan and Cleary have suggested a period of one week to two weeks during which time the eye becomes more amenable to vitreous surgery.[5] This allows maturation of this cell bolus. It may be therefore, in the clinical setting as trauma is cared for today, that a cell bolus which attacks not only immediately dividing cells with a cytotoxic agent, such as methyltrexate and 5-FU, but also attacks the

myofibroblast contraction and breaking down of cellular junctions may be most beneficial.

It is always a concern to interpret rabbit clinical data and apply this to the primate or human condition. For that reason, further clinical study on an animal model would seem reasonable, but in this evaluation it would make sense that a broad spectrum of pharmacologic activity may be needed to attack the multiplicity of cellular circumstances within the offending intravitreal proliferating bolus of cells. The results of our study would suggest that such a bolus of methyltrexate or 5-FU as a cytotoxic agent in addition to prostaglandin PGE1 or d-penicillamine as an agent to suppress myofibroblastic contraction and cell attachment may be the most effective combination chemotherapy to suppress intraocular cellular proliferation following trauma.

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GLOSSARY

Hypocellular gel contraction: Hypocellular gel contraction involves the cell small in number having an effect on the large amount of vitreous collagen organizing this gel and showing an effective contraction of collagen and subsequent retinal detachment assume a tight adhesion between the collagen and underlying neurosensory retina.

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